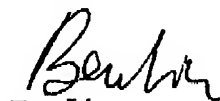


Claim Listing

Claim 1 (currently amended): The deleted matter is marked by strike-through. The added matter is marked by underlining.

Claim 2 – 89 (original)



Ben Liu

Inventor of Application 10/055878

Office Phone: 919-468-5552 extension 222

Cell Phone: 919-244-7975

Office Address: Ben Liu, Ph.D.
Bio-Informatics Group, Inc.
2000 Regency Parkway, Suite 395
Cary, North Carolina 27511

Home Address: Ben Liu
5720 Thistleton Lane
Raleigh, North Carolina 27606

RECEIVED
CENTRAL FAX CENTER

JUN 23 2004

OFFICIAL

Amended Claims

What is claimed is:

1. An article in FIGs 1 and 3 comprising: ~~at least two plates; at least a top plate 30, a bottom plate 40, and a center plate 20~~ wherein the center plate 20 each plate defines a plurality of cylindrical capillaries 50, each capillary having a pair of opposed ends, with at least one capillary comprising a reagent inlet 52 and at least one capillary comprising a reagent outlet 54; ~~the plate the top plate 30 and bottom plate 40~~ further defining a plurality of channels 60 oriented substantially perpendicularly to the capillaries 50 and configured to selectively operably

connect adjacent capillaries so as to form a continuous passage from the reagent inlet 52 to the reagent outlet 54, the channels being further configured to direct the reagent into a capillary at one end thereof and from the capillary at the other end thereof such that the reagent flows through substantially the length of the capillary and serially through all of the capillaries defined by the plate; and wherein said plates are positioned to substantially align the plurality of cylindrical capillaries from a first plate and a second plate.

2. The article according to claim 1, wherein the plates are substantially flat and further comprise a medial member disposed between and operably engaging opposing distal members.
3. The article according to claim 2, wherein the medial member defines the capillaries and the channels.
4. The article according to claim 2, wherein the medial member defines the capillaries and the distal members define the channels.
5. The article according to claim 2, further comprising at least one securing member configured to secure the distal members to the medial member in sealing relation.
6. The article according to claim 1, wherein the capillaries are disposed in an array.
7. The article according to claim 1, wherein the capillaries are between about 5 microns and about 11000 microns in diameter.
8. The article according to claim 1, wherein the capillaries are each configured to have a voltage applied across the ends thereof so as to form an electrostatic pump capable of causing the reagent to flow in a corresponding direction there between.

9. The article according to claim 8, wherein the voltage is reversible such that the flow of the reagent is capable of being selectively reversed.
10. The article according to claim 1, wherein the capillaries are each configured to have a bio sample deposited on the inner wall of the capillary such that the biosample is assayed by a reagent flowing through the capillary.
11. The article according to claim 1, wherein the plate is comprised of at least one of a semiconductor material and a polymeric material.
12. The article according to claim 11, wherein the plate is comprised of at least one of silicon and an injection-moldable polymeric material.
13. The article according to claim 11, wherein the plate is comprised of a polymeric material when the plate defines a capillary density up to 110 about 2,000 capillaries per square centimeter.
14. The article according to claim 11, wherein the plate is comprised of a semiconductor material when the plate defines a capillary density between about 2,000 capillaries per square centimeter and about 200,000 capillaries per square centimeter.
15. The article according to claim 1, which comprises at least 10 to 100 plates.
16. The article according to claim 1, which comprises at least 100 plates.
17. The article according to claim 1, which further comprises a volume-reducing arrayer apparatus, wherein said volume-reducing arrayer apparatus comprises: at least one plate disposed between the reservoir and the substrate and in communication with the reservoir, the at least one plate defining at least one plate capillary extending toward the substrate, the at least one plate capillary being

configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom; and a flow control device disposed between the at least one plate and the substrate and in communication with the at least one plate, the flow control device defining at least one flow control capillary corresponding to the at least one plate capillary and extending toward the substrate, the at least one flow control capillary being configured to have a reduced volume with respect to the at least one plate capillary, the flow control device being further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary, from the at least one plate capillary to the substrate.

18. The article according to claim 17, wherein the at least one flow control capillary is configured to have a diameter smaller than the diameter of the plate capillary such that the smaller diameter of the flow control capillary provides a reduced volume per unit length with respect to the plate capillary.
19. The article according to claim 17, wherein the at least one plate defines a plurality of plate capillaries arranged in an array.
20. The article according to claim 19, wherein the flow control device defines a plurality of flow control capillaries arranged in an array corresponding to the plate capillary array.
21. The article according to claim 20, wherein at least one of the plate and the flow control device defines a plurality of channels configured such that each channel operably connects one plate capillary in the plate capillary array to one corresponding flow control capillary in the flow control device array.

22. The article according to claim 17, wherein the at least one plate comprises a first plate and a second plate, with each plate having a solution entrance surface and a solution exit surface, and wherein the solution exit surface of the first plate is configured to operably engage the solution entrance surface of the second plate.
23. The article according to claim 22, wherein the first plate defines a plurality of first plate capillaries arranged in an array, the array further comprising a first portion of first plate capillaries and a second portion of first plate capillaries.
24. The article according to claim 23, wherein the solution exit surface of the first plate further defines a plurality of first plate channels,- with each first plate channel extending from one capillary in the first portion of first plate capillaries to a corresponding indentation in a plurality of first plate indentations also defined by the solution exit surface of the first plate, the first plate indentations also being arranged in an array.
25. The article according to claim 24, wherein the second plate defines a plurality of second plate capillaries arranged in an array, the array further comprising a first part of the second plate capillaries corresponding to the second portion of the first plate capillaries and a second part of second plate capillaries corresponding to the first plate indentations.
26. An arrayer apparatus according to claim 25, wherein the solution exit surface of the second plate further defines a plurality of second plate channels, with each second plate channel extending from one capillary in the first part of the second plate capillaries to a corresponding indentation in a plurality of second plate

indentations also defined by the solution exit surface of the second plate, the second plate indentations also being arranged in an array.

27. The article according to claim 26, wherein the flow control device defines a plurality of flow control capillaries arranged in an array, the flow control capillaries corresponding to the second plate indentations and to the second part of the second plate capillaries corresponding to the first plate indentations.
28. The article according to claim 17, further comprising a stamper head disposed between the flow control device and the substrate and in communication with the flow control device, the stamper head defining a plurality of stamper capillaries arranged in an array and corresponding to the flow control capillaries, the stamper head being configured to channel the predetermined amount of the solution from the flow control device to the substrate.
29. The article according to claim 28, wherein the stamper capillaries are configured to have a reduced volume with respect to the flow control capillaries.
30. The article according to claim 29, wherein the stamper capillaries are each configured to have a diameter smaller than diameter of each flow control capillary such that smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the flow control capillary.
31. The article according to claim 17, wherein the flow control device comprises at least one of a pump and a valve.
32. The article according to claim 17, wherein the flow control capillaries are each configured to have a voltage applied between two points along the length thereof

so as to form an electrostatic pump capable of causing the solution to flow therealong.

33. The article according to claim 32, wherein the voltage is capable of being adjusted so as to form an electrostatic valve capable of selectively preventing flow of the solution through the flow control capillaries.
34. The article according to claim 33, wherein the voltage is capable of being controlled such that only a predetermined amount of the solution flows through the flow control capillaries.
35. The article according to claim 17, wherein at least one of the flow control device and the at least one plate are comprised of silicon.
36. The article according to claim 1, which further comprises a volume-reducing arrayer apparatus, wherein said volume-reducing arrayer apparatus comprises: a reservoir for containing the solution; at least one arrayer block disposed between the reservoir and the substrate and in communication with the reservoir, the at least one arrayer block defining at least one arrayer capillary extending toward the substrate, the at least one arrayer capillary being configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom; a flow control device disposed between the at least one arrayer block and the substrate and in communication with the at least one arrayer block, the flow control device defining at least one flow control capillary corresponding to the at least one arrayer capillary, extending toward the substrate, and being configured to have a reduced volume with respect to the at least one plate capillary, the flow control device being further configured to control the flow of a

predetermined amount of the solution through the at least one flow control capillary; and a stamper head disposed between the flow control device and the substrate and in communication with the flow control device, the stamper head defining at least one stamper capillary corresponding to the at least one flow control capillary and extending toward the substrate, the at least one stamper capillary being configured to have the predetermined amount of the solution channeled therethrough by the flow control device, from the at least one flow control capillary to the substrate.

37. The article according to claim 36, wherein the at least one flow control capillary is configured to have a diameter smaller than the diameter of the at least one arrayer capillary such that smaller diameter of the flow control capillary provides a reduced volume per unit length with respect to the arrayer capillary.
38. The article according to claim 36, wherein the at least one stamper capillary is configured to have a diameter smaller than the diameter of the at least one flow control capillary such that smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the flow control capillary.
39. The article according to claim 36, wherein the at least one arrayer block defines a plurality of arrayer capillaries arranged in an array.
40. The article according to claim 39, wherein the flow control device defines a plurality of flow control capillaries arranged in an array corresponding to the arrayer capillary array.

41. The article according to claim 39, wherein the stamper head defines a plurality of stamper capillaries arranged in an array corresponding to the flow control capillary array.
42. The article according to claim 39, wherein at least one of the flow control device and the at least one arrayer block defines a plurality of channels configured such that each channel operably connects one arrayer capillary in the arrayer capillary array to one corresponding flow control capillary in the flow control device array.
43. The article according to claim 36, wherein the at least one arrayer block comprises a first arrayer block and a second arrayer block, with each arrayer block having a solution entrance surface and a solution exit surface, and wherein the solution exit surface of the first arrayer block is configured to operably engage the solution entrance surface of the second arrayer block.
44. The article according to claim 43, wherein the first arrayer block defines a plurality of first arrayer capillaries arranged in an array, the array further comprising a first portion of first arrayer capillaries and a second portion of first arrayer capillaries.
45. The article according to claim 44, wherein the solution exit surface of the first arrayer block further defines a plurality of first arrayer channels, with each first arrayer channel extending from one capillary in the first portion of first arrayer capillaries to a corresponding indentation in a plurality of first arrayer indentations also defined by the solution exit surface of the first arrayer block, the first arrayer indentations also being arranged in an array.

46. The article according to claim 45, wherein the second arrayer block defines a plurality of second arrayer capillaries arranged in an array, the array further comprising a first part of the second arrayer capillaries corresponding to the second portion of the first arrayer capillaries and a second part of second arrayer capillaries corresponding to the first arrayer indentations.
47. The article according to claim 46, wherein the solution exit surface of the second arrayer block further defines a plurality of second arrayer channels, with each second arrayer channel extending from one capillary in the first part of the second arrayer capillaries to a corresponding indentation in a plurality of second arrayer indentations also defined by the solution exit surface of the second arrayer block, the second arrayer indentations also being arranged in an array.
48. The article according to claim 47, wherein the flow control device defines a plurality of flow control capillaries arranged in an array, the flow control capillaries corresponding to the second arrayer indentations and to the second part of the second arrayer capillaries corresponding to the first arrayer indentations.
49. The article according to claim 36, wherein the flow control device comprises at least one of a pump and a valve.
50. The article according to claim 36, wherein the flow control capillaries are each configured to have a voltage applied between two points along the length thereof so as to form an electrostatic pump capable of causing the solution to flow therealong.

51. The article according to claim 50, wherein the voltage is capable of being adjusted so as to form an electrostatic valve capable of selectively preventing flow of the solution through the flow control capillaries.
52. The article according to claim 50, wherein the voltage is capable of being controlled such that only a predetermined amount of the solution flows through the flow control capillaries.
53. The article according to claim 36, wherein at least one of the stamper head, the flow control device, and the at least one arrayer block are comprised of silicon.
54. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising: forming a medial plate having a pair of opposed surfaces, the medial plate defining a plurality of cylindrical capillaries with each capillary having a pair of opposed ends; forming a pair of end plates, each end plate being configured to operably engage one of the opposed surfaces of the medial plate, each end plate defining a series of channels configured so as to be oriented substantially perpendicularly to the capillaries and to selectively connect adjacent capillaries at the ends thereof when the end plates are operably engaged with the medial plate; securing the end plates to the opposed surfaces of the medial plate so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate; and aligning at least two of said medial plates to align the plurality of cylindrical capillaries from a first medial plate and a second medial plate to form an essentially continuous passage.

55. The method according to claim 54, wherein forming a medial plate further comprises forming a medial plate defining a plurality of cylindrical capillaries disposed in an array.
56. The method according to claim 54, wherein securing the end plates to the opposed surfaces of the medial plate further comprises securing the end plates to the opposed surfaces of the medial plate with at least one securing member.
57. The method according to claim 54, wherein forming a medial plate comprises injection molding a polymeric material into said medial plate.
58. The method according to claim 54, wherein forming a pair of end plates comprises injection molding a polymeric material into said pair of end plates.
59. The method according to claim 54, comprising aligning the plurality of cylindrical capillaries of at least 10 medial plates.
60. The method according to claim 54, comprising aligning the plurality of cylindrical capillaries of from 10 to 100 medial plates.
61. The method according to claim 54, comprising aligning the plurality of cylindrical capillaries of at least 100 medial plates.
62. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising: providing a mold defining a medial plate having a pair of opposed surfaces, the mold having a plurality of cylindrical rods, each rod having a pair of opposed ends, the mold further having a series of connecting members oriented substantially perpendicularly to the rods about the opposed surfaces of the medial plate and selectively connecting adjacent rods at the ends thereof; introducing a polymeric material into the mold so as to form the medial

plate, the medial plate thereby defining a plurality of capillaries corresponding to the rods and a plurality of channels corresponding to the connecting members; releasing the medial plate from the mold; sealing the opposed surfaces of the medial plate with corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate; and aligning at least two of said medial plates to align the plurality of cylindrical capillaries from a first medial plate and a second medial plate to form an essentially continuous passage.

63. The method according to claim 62, wherein providing a mold further comprises providing a mold having a plurality of cylindrical rods disposed in an array.
64. The method according to claim 62, wherein sealing the opposed surfaces of the medial plate with corresponding end plates further comprises sealing the opposed surfaces of the medial plate with corresponding end plates and at least one securing member configured to secure the end plates to the medial plate.
65. The method according to claim 62, wherein introducing a polymeric material into the mold further comprises introducing an injection-moldable polymeric material into the mold.
66. The method according to claim 62, wherein providing a mold further comprises providing a mold having up to about 2,000 capillaries per square centimeter to produce a medial plate having a corresponding capillary density.

67. The method according to claim 62, further comprising forming the end plates by injection molding of a polymeric material prior to sealing the opposed surfaces of the medial plate.
68. The method according to claim 62, comprising aligning the plurality of cylindrical capillaries of at least 10 medial plates.
69. The method according to claim 62, comprising aligning the plurality of cylindrical capillaries of from 10 to 100 medial plates.
70. The method according to claim 62, comprising aligning the plurality of cylindrical capillaries of at least 100 medial plates.
71. A method of fabricating a biochip defining a plurality of connected capillaries, said method comprising: etching a plurality of cylindrical capillaries in a medial plate having a pair of opposed surfaces, each capillary having a pair of opposed ends; selectively etching a plurality of channels, oriented substantially perpendicularly to the capillaries, between adjacent capillaries on each of the opposed surfaces of the medial plate; sealing the opposed surfaces of the medial plate with corresponding end plates so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the medial plate; and aligning at least two of said medial plates to align the plurality of cylindrical capillaries from a first medial plate and a second medial plate to form an essentially continuous passage.

72. The method according to claim 71, wherein etching a plurality of cylindrical capillaries in a medial plate further comprises etching a plurality of cylindrical capillaries disposed in an array in a medial plate.
73. The method according to claim 71, wherein sealing the opposed surfaces of the medial plate with corresponding end plates further comprises sealing the opposed surfaces of the medial plate with corresponding end plates and at least one securing member configured to secure the end plates to the medial plate.
74. The method according to claim 71, further comprising patterning a photoresist deposited on the medial plate so as to define portions of the medial plate to be etched, the portions corresponding to at least one of the plurality of capillaries and the plurality of channels, prior to etching the plurality of capillaries and etching the plurality of channels.
75. The method according to claim 71, wherein etching a plurality of capillaries further comprises etching a plurality of capillaries having a capillary density of between about 2,000 capillaries per square centimeter and about 200,000 capillaries per square centimeter.
76. The method according to claim 71, wherein etching a plurality of capillaries in a medial plate further comprises etching a plurality of capillaries in a medial plate comprised of a semiconductor material.
77. The method according to claim 71, wherein etching a plurality of capillaries in a medial plate further comprises etching a plurality of capillaries in a medial plate comprised of a silicon.

78. The method according to claim 71, comprising aligning the plurality of cylindrical capillaries of at least 10 medial plates.
79. The method according to claim 71, comprising aligning the plurality of cylindrical capillaries of from 10 to 100 medial plates.
80. The method according to claim 71, comprising aligning the plurality of cylindrical capillaries of at least 100 medial plates.
81. A method of testing multiple sample parallel bioassays, comprising: providing a biochip comprising at least two plates, where each plate defines a plurality of cylindrical capillaries having opposed ends and being selectively operably connected by a series of channels oriented substantially perpendicularly thereto and about the ends thereof so as to form a continuous passage from a reagent inlet capillary to a reagent outlet capillary, the passage extending substantially the length of each capillary and serially through all of the capillaries defined by the biochip, and where said plates are positioned to substantially align the plurality of cylindrical capillaries from a first plate and a second plate; immobilizing a biosample on the inner walls of each of the cylindrical capillaries; flowing a test sample through each of said cylindrical capillaries; and assaying the presence or absence of an interaction between said immobilized biosample and said test sample.
82. The method according to claim 81, wherein flowing a test sample comprises applying a voltage across the ends of each capillary so as to electrostatically pump the test sample in a corresponding flow direction through the capillaries.

83. The method according to claim 81, wherein flowing a test sample comprises selectively reversing the flow direction of the test sample by reversing the voltage across the ends of each capillary.
84. The method according to claim 81, wherein the biosample immobilized on the plurality of cylindrical capillaries of a first plate is different from the biosample immobilized on the plurality of cylindrical capillaries of a second plate.
85. The method according to claim 81, wherein the biosample is selected from the group consisting of an antibody, an antigen, and a nucleic acid.
86. The method according to claim 81, wherein immobilizing a biosample on the inner walls of each of the capillaries comprises delivering portions of the biosample solution from a microtiter plate containing the biosample solution to a plurality of first capillaries, the first capillaries being arranged in an array, each first capillary having a predetermined diameter; delivering at least a portion of the biosample solution from each of the first capillaries to a corresponding second capillary in a plurality of second capillaries defined by a second plate, the second capillaries being arranged in an array corresponding to the first capillary array, each of the second plate capillaries having a diameter smaller than the first plate capillary diameter such that the smaller diameter of the second capillary provides a reduced volume per unit length of the solution therein with respect to the first capillary; and delivering at least a portion of the biosample solution from each of the second capillaries to the inner walls of each of the plurality of cylindrical capillaries of said first and second plate.

87. The method according to claim 81, wherein flowing a test sample through each of said cylindrical capillaries delivering portions of the test sample solution from a microtiter plate containing the test sample solution to a plurality of first capillaries, the first capillaries being arranged in an array, each first capillary having a predetermined diameter; delivering at least a portion of the test sample solution from each of the first capillaries to a corresponding second capillary in a plurality of second capillaries defined by a second plate, the second capillaries being arranged in an array corresponding to the first capillary array, each of the second plate capillaries having a diameter smaller than the first plate capillary diameter such that the smaller diameter of the second capillary provides a reduced volume per unit length of the solution therein with respect to the first capillary; and delivering at least a portion of the test sample solution from each of the second capillaries to the inner walls of each of the plurality of cylindrical capillaries of said first and second plate.
88. A 4D biochip, comprising: m 3D biochip means, wherein m is an integer from 2 to 100,000 wherein each pair of adjacent 3D biochip means are operably connected by aligning capillaries present in one of said pair with capillaries present in the other of said pair.
89. The 4D biochip of claim 88, wherein each of said m 3D biochip means contains n capillaries passing there through, wherein n is an integer from 2 to 100,000.



Ben Liu
Inventor of Application 10/055878
Office Phone: 919-468-5552 extension 222
Cell Phone: 919-244-7975